Rec'd PCT/PTO 26 MAY 1998

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		Attorney's Docket Number P1103/0015 U.S. Application No.
International Application. No.	International Filing Date	Priority Date Claimed
PCT/EP97/05070	September 16, 1997	September 27, 1996

Title of Invention:
USE OF 1-HYDROXY-2-PYRIDONES FOR THE TREATMENT OF SEBORRHEIC DERMATITIS

Applicant(s) For DO/EO/US:
Manfred BOHN, Karl Theodor KRAEMER and Astrid MARKUS

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.

16. [ ] Other items or information:
    a. [ ] Verified Small Entity Statement.
    b. [ ] Copy of Notification of Missing Requirements.

U.S. APPLICATION NO.	INTERNATIONAL APPLICATION NO.	ATTORNEY DOCKET NUMBER
	PCT/EP97/05070	07103.0015

17. [X] The following fees are submitted:	CALCULATIONS
Basic National Fee (37 CFR 1.492(a)(1)-(5)):	
Search Report has been prepared by the EPO or JPO.....$930.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$720.00	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$790.00	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$1,070.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4).....$ 98.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$930.00**
Surcharge of $130.00 for furnishing the oath or declaration later than **[ ] 20 [ ] 30** months from the earliest claimed priority date (37 CFR 1.492(e)).	$

Claims	Number Filed	Number Extra	Rate	
Total Claims	18 -20=		X $22.00	$
Independent Claims	3 - 3=		X $82.00	$
Multiple dependent claim(s) (if applicable)			+$270.00	$
TOTAL OF ABOVE CALCULATIONS =				**$930.00**
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28)				$
SUBTOTAL =				**$930.00**
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	$
TOTAL NATIONAL FEE =				**$930.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31).			$40.00 per property +	**$**
TOTAL FEES ENCLOSED =				**$930.00**
			Amount to be refunded	$
			charged	$

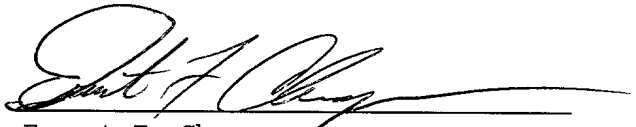
a. [X] A check in the amount of **$930.00** to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0916. A duplicate copy of this sheet is enclosed.

The Commissioner is hereby authorized to charge any other fees due under 37 C.F.R. §1.16 or §1.17 during the pendency of this application to our Deposit Account No. 06-0916.

SEND ALL CORRESPONDENCE TO:
Finnegan, Henderson, Farabow
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315
EFC/FPD/rgm



Ernest F. Chapman
Reg. No. 25,961

Submitted: May 26, 1998

09/077194
88 Rec'd PCT/PTO 26 MAY 1998

PATENT
Attorney Docket No. 7103.0015

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Manfred BOHN, et al.	)	
	)	
Serial No.: New U.S. National Stage Application of PCT Appln. No. PCT/EP97/05070	)	Group Art Unit: Unknown
	)	
Filed: May 26, 1998	)	
	)	Examiner: Unknown
	)	
For: USE OF 1-HYDROXY-2-PYRIDONE FOR THE TREATMENT OF SEBORRHEIC DERMATITIS	)	

Box PCT
Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to the examination of the above application, please amend this application as follows:

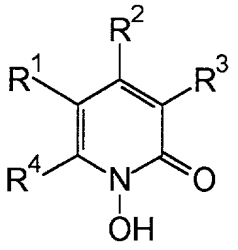
IN THE CLAIMS:

Please delete claims 1-13 without prejudice or disclaimer and add new claims 14-31 as follows:

attached to the NOV 1998

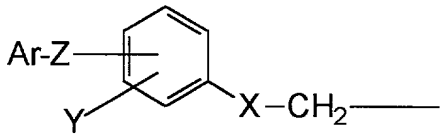
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--14. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis comprising the step of administering to the patient an efficacious amount of a 1-hydroxy-2-pyridone of formula I, wherein the 1-hydroxy-2-pyridone is present in free form or as a pharmaceutically acceptable salt:



(I)

where R^1, R^2, and R^3, which are identical or different, are H or alkyl having 1 to 4 carbon atoms, and R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms or a radical of formula II:



(II)

where:

X is S or O;

Y is H, or 1 or 2 identical halogen atoms, or a mixture of 2 different halogen atoms;

Z is a single bond, or

a bivalent radical comprising

(1) O, or

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(2) S, or

(3) $-CR^2-$, where R is H or (C_1-C_4)-alkyl, or

(4) a bivalent radical having from 2 to 10 carbon atoms linked in the form of a chain, which optionally further comprises one or more of the following:

(i) a carbon-carbon double bond, or

(ii) O, S, or a mixture thereof, wherein if 2 or more O or S atoms or a mixture thereof are present, each O or S atom is separated by at least 2 carbon atoms; and,

in any of the foregoing bivalent radicals, the free valences of the carbon atoms of said bivalent radical are saturated by H, (C_1-C_4)-alkyl, or a mixture thereof; and

Ar is an aromatic ring system having one or two rings which can be substituted by one, two, or three radicals, which may be identical or different, which are halogen, methoxy, (C_1-C_4)-alkyl, trifluoromethyl, or trifluoromethoxy.

15. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 14 in which the 1-hydroxy-2-pyridone of formula I comprises Ar as a bicyclic system derived from biphenyl, diphenylalkane, or diphenyl ether.

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16. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 14 in which the 1-hydroxy-2-pyridone of formula I comprises a cyclohexyl radical in the R^4 position.

17. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 14 in which the 1-hydroxy-2-pyridone of formula I comprises an octyl radical of the formula $-CH_2-CH(CH_3)-CH_2-C(CH_3)_3$ in the R^4 position.

18. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 14 in which the 1-hydroxy-2-pyridone of formula I is 1-hydroxy-4-methyl-6-[4-(4-chlorophenoxy)phenoxymethyl]-2(1H)pyridone, 1-hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone, or 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)pyridone, or a pharmaceutically acceptable salt of any of the foregoing.

19. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 14 in which the 1-hydroxy-2-pyridone of formula I or the pharmaceutically acceptable salt thereof is administered to the patient in a pharmaceutical composition in the form of a hair lotion, shampoo, cream, ointment, or gel preparation.

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20. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 19 in which the pharmaceutical composition further comprises at least one anionic surfactant.

21. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 19 in which the pharmaceutical composition further comprises at least one cationic surfactant.

22. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 19 in which the pharmaceutical composition further comprises at least one nonionic surfactant.

23. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 19 in which the pharmaceutical composition further comprises at least one cationic surfactant.

24. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 19 in which the pharmaceutical composition further comprises at least one amphoteric surfactant.

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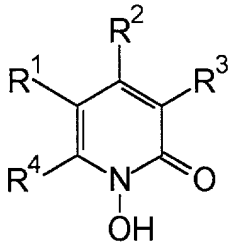
25. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 19 in which the pharmaceutical composition further comprises a mixture of anionic, cationic, nonionic, or amphoteric surfactants.

26. A method of treating a human or animal patient in need of treatment for seborrheic dermatitis as claimed in claim 19 in which the pharmaceutical composition has a pH from about 4.5 to about 6.5.

Document Page 6 of 10

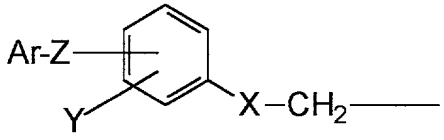
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27. A pharmaceutical composition useful for treating a human or animal patient in need of treatment for seborrheic dermatitis comprising an efficacious amount of a 1-hydroxy-2-pyridone of formula I, wherein the 1-hydroxy-2-pyridone is present in free form or as a pharmaceutically acceptable salt:



(I)

where R^1, R^2, and R^3, which are identical or different, are H or alkyl having 1 to 4 carbon atoms, and R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms or a radical of formula II:



(II)

where:

X is S or O;

Y is H, or 1 or 2 identical halogen atoms, or a mixture of 2 different halogen atoms;

Z is a single bond, or

a bivalent radical comprising

(1) O, or

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(2) S, or

(3) $-CR^2-$, where R is H or (C_1-C_4)-alkyl, or

(4) a bivalent radical having from 2 to 10 carbon atoms linked in the form of a chain, which optionally further comprises one or more of the following:

(i) a carbon-carbon double bond, or

(ii) O, S, or a mixture thereof, wherein if 2 or more O or S atoms or a mixture thereof are present, each O or S atom is separated by at least 2 carbon atoms; and,

in any of the foregoing bivalent radicals, the free valences of the carbon atoms of said bivalent radical are saturated by H, (C_1-C_4)-alkyl, or a mixture thereof; and

Ar is an aromatic ring system having one or two rings which can be substituted by one, two, or three radicals, which may be identical or different, which are halogen, methoxy, (C_1-C_4)-alkyl, trifluoromethyl, or trifluoromethoxy; and

the pharmaceutical composition further comprises at least one anionic, cationic, nonionic, or amphoteric surfactant, or a mixture thereof.

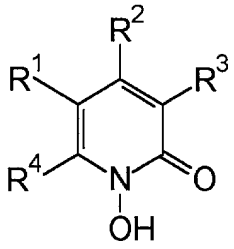
28. A pharmaceutical composition as claimed in claim 27 in which the pharmaceutical composition has a pH from about 4.5 to about 6.5.

29. A pharmaceutical composition as claimed in claim 27 in which the 1-hydroxy-2-pyridone of formula I has a concentration from about 0.2% to about 10%.

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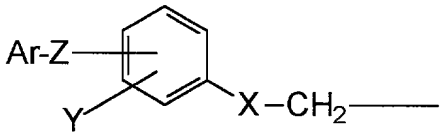
30. A pharmaceutical composition as claimed in claim 27 in which the 1-hydroxy-2-pyridone of formula I has a concentration from about 0.5% to 2%.

31. A method of preparing a pharmaceutical composition useful for treating a human or animal patient in need of treatment for seborrheic dermatitis comprising the step of combining at least one anionic, cationic, nonionic, or amphoteric surfactant, or a mixture thereof, together with an efficacious amount of a 1-hydroxy-2-pyridone of formula I, wherein the 1-hydroxy-2-pyridone is present in free form or as a pharmaceutically acceptable salt:



(I)

where R^1, R^2, and R^3, which are identical or different, are H or alkyl having 1 to 4 carbon atoms, and R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms or a radical of formula II:



(II)

where:

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X is S or O;

Y is H, or 1 or 2 identical halogen atoms, or a mixture of 2 different halogen atoms;

Z is a single bond, or

a bivalent radical comprising

(1) O, or

(2) S, or

(3) $-CR^2-$, where R is H or (C_1-C_4)-alkyl, or

(4) a bivalent radical having from 2 to 10 carbon atoms linked in the form of a chain, which optionally further comprises one or more of the following:

(i) a carbon-carbon double bond, or

(ii) O, S, or a mixture thereof, wherein if 2 or more O or S atoms or a mixture thereof are present, each O or S atom is separated by at least 2 carbon atoms; and,

in any of the foregoing bivalent radicals, the free valences of the carbon atoms of said bivalent radical are saturated by H, (C_1-C_4)-alkyl, or a mixture thereof; and

Ar is an aromatic ring system having one or two rings which can be substituted by one, two, or three radicals, which may be identical or different, which are halogen, methoxy, (C_1-C_4)-alkyl, trifluoromethyl, or trifluoromethoxy.

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REMARKS

This application represents entry into the U.S. national phase of International Application Serial No. PCT/EP97/05070 under the provisions of the Patent Cooperation Treaty. The original thirteen claims are deleted, and new claims 14 through 31 have been added to conform with United States claiming convention and to clearly set forth the claimed invention. Care has been taken so that no new matter has been introduced into the claims.

The Commissioner is hereby authorized to charge any additional filing fees due and any other fees due under 37 C.F.R. § 1.16 or § 1.17 during the pendency of this application to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: _____
Allen R. Jensen
Reg. No. 28,224

Dated: May 26, 1998

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Use of 1-hydroxy-2-pyridones for the treatment of seborrheic dermatitis

Seborrheic dermatitis is understood as meaning a disorder of the scalp which differs from simple dandruff by the presence of erythema as a sign of inflammation, by the greater degree of scaling with occasional itching and burning, and by the occurrence of eczematous changes to other body sites. It can occur in the form of patches, but also more frequently affects the whole scalp and often includes, beyond the hairline, the forehead, around the neck and the ears. In severe cases, the scalp can have a secondary infection, and the changes can then exhibit a spongy consistency, vesicle and crust formation and can weep.

Seborrheic dermatitis frequently occurs even in infancy and usually remits spontaneously at an age of 8-12 months. The scalp changes consisting of erythema, scaling and occasionally vesicles and crusts in infants can regress spontaneously within a few weeks, intermittently reoccur or persist during the entire childhood. They are frequently combined with a similar process around the eyelids, nose and ears. Later, the condition usually occurs after puberty and can last for the whole life or even increase in strength. Approximately 1-3% of the population are affected by this illness.

It is known that 1-hydroxy-2-pyridones and their salts exhibit activity against normal dandruff which is characterized by a clinically noninflammatory scaling of the scalp occurring in nearly all people (DE 22 34 009).

The most promising type of treatment of seborrheic dermatitis until now was the topical application of corticosteroid preparations, but more recently topical therapy with antimycotic substances has gained importance.

While corticosteroid preparations display their activity exclusively via an effect on the inflammatory process, the antimycotic substances such as ketoconazole are active exclusively against the yeast fungi of the strain Pityrosporum which is assumed to be the cause of seborrheic dermatitis. The 1-hydroxy-2-pyridones according to the invention, however, combine the properties of both classes of substance in one substance and exhibit both antiinflammatory action and antimycotic activity against Pityrosporum strains.

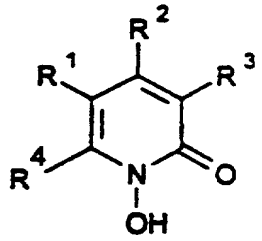
In comparison to ketoconazole, the substances according to the invention - even after only a short topical contact time - concentrate rapidly in the skin layers which are relevant for fungal growth and thus contribute to a rapid cure.

While ketoconazole is inactive in vitro against gram-positive bacteria (Kinsman et al., J. Med. Microbiol. (1983) 16, No. 2, IV), the hydroxy-pyridones according to the invention exhibit activity against gram-positive and gram-negative aerobic and anaerobic bacteria (Dittmar et al., Arzneim.-Forschung, (1981) 31 (II), No. 8a, pp. 1317-1322). With respect to the treatment of secondarily infected cases, this is an extremely important finding.

Compared with ketoconazole, the compounds used according to the invention furthermore have very crucial advantages with respect to their processing possibilities in pharmaceutical preparations. On account of their solubility in water, alcohols and aqueous-alcoholic solutions, the preparation of hair lotions and transparent gel preparations is possible without problems.

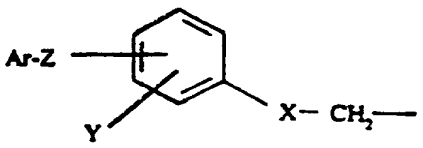
The preparations according to the invention can also be employed for the treatment of Pityriasis versicolor, a superficial, noninflammatory skin fungus disorder on the trunk.

The invention therefore relates to the use of 1-hydroxy-2-pyridones of the formula I



(I)

in which R^1, R^2 and R^3, which are identical or different, are a hydrogen atom or alkyl having 1-4 carbon atoms, and
R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms or a radical of the formula II



(II),

where

X is S or O,

Y is a hydrogen atom or up to 2 halogen atoms such as chlorine and/or bromine,

Z is a single bond or the bivalent radicals O, S, $-CR^2-$ (R = H or (C_1-C_4)-alkyl) or other bivalent radicals having 2-10 carbon and, if appropriate, oxygen and/or sulfur atoms linked in the form of a chain, where - if the radicals contain 2 or more oxygen and/or sulfur atoms - the latter must be separated from one another by at least 2 carbon atoms and where 2 adjacent carbon atoms can also be linked to one another by a double bond and the free valences of the carbon atoms are saturated by H and/or (C_1-C_4)-alkyl groups,

Ar is an aromatic ring system having up to two rings which can be substituted by up to three radicals from the group consisting of fluorine, chlorine, bromine, methoxy, (C_1-C_4)-alkyl, trifluoromethyl and trifluoromethoxy, in free or in salt form,

for the production of a pharmaceutical for the treatment of seborrheic dermatitis.

In the radicals "Z", the carbon chain members are preferably CH_2 groups. If the CH_2 groups are substituted by C_1-C_4-alkyl groups, CH_3 and C_2H_5 are preferred substituents. Exemplary radicals "Z" are:

-O-, -S-, $-CH_2-$, $-(CH_2)_m-$ (m = 2-10), $-C(CH_3)_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S-$, $-SCH_2-$, $-SCH(C_2H_5)-$, $-CH=CH-CH_2O-$, $-O-CH_2-CH=CH-CH_2O-$, $-OCH_2-CH_2O-$, $-OCH_2-CH_2CH_2O-$, $-SCH_2CH_2CH_2S-$, $-SCH_2CH_2CH_2CH_2O-$, $-SCH_2CH_2OCH_2CH_2O-$, $-SCH_2CH_2OCH_2CH_2O-CH_2CH_2S-$ or $-S-CH_2-C(CH_3)_2-CH_2-S-$.

The radical "S" is a sulfur atom, the radical "O" is an oxygen atom. The term "Ar" denotes phenyl or fused systems such as naphthyl, tetrahydronaphthyl and indenyl, and also isolated systems as such, which are derived from biphenyl, diphenylalkanes, diphenyl ethers and diphenyl thioethers.

EP 1 504 760 A1 20050209

In the formula I, the hydrocarbon radial R^4 is an alkyl or cyclohexyl radical which can also be bonded to the pyridone ring via a methylene or ethylene group or can contain an endomethyl group. R^4 can also be an aromatic radical which, however, is preferably bonded to the pyridone radical via at least one aliphatic carbon atom.

Important representatives of the class of compounds characterized by the formula I are:

6-[4-(4-chlorophenoxy)phenoxymethyl]-1-hydroxy-4-methyl-2-pyridone, 6-[4-(2,4-dichlorophenoxy)phenoxymethyl]-1-hydroxy-4-methyl-2-pyridone, 6-(biphenyl-4-oxymethyl)-1-hydroxy-4-methyl-2-pyridone, 6-(4-benzyl-phenoxymethyl)-1-hydroxy-4-methyl-2-pyridone, 6-[4-(2,4-dichlorobenzyl-oxy)phenoxymethyl]-1-hydroxy-4-methyl-2-pyridone, 6-[4-(4-chloro-phenoxy)phenoxymethyl]-1-hydroxy-3,4-dimethyl-2-pyridone, 6-[4-(2,4-dichlorobenzyl)phenoxymethyl]-1-hydroxy-3,4-dimethyl-2-pyridone, 6-[4-cinnamyloxy)phenoxymethyl]-1-hydroxy-4-methyl-2-pyridone, 1-hydroxy-4-methyl-6-[4-(4-trifluoromethylphenoxy)phenoxymethyl]-2-pyridone, 1-hydroxy-4-methyl-6-cyclohexyl-2-pyridone, 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone, 1-hydroxy-4-methyl-6-n-hexyl-, -6-isohexyl-, -6-n-heptyl- or -6-isoheptyl-2-pyridone, 1-hydroxy-4-methyl-6-octyl- or -6-isooctyl-2-pyridone, in particular 1-hydroxy-4-methyl-6-cyclohexylmethyl- or -6-cyclohexylethyl-2-pyridone, where the cyclohexyl radical can in each case also carry a methyl radical, 1-hydroxy-4-methyl-6-(2-bicyclo-[2,2,1]heptyl)-2-pyridone, 1-hydroxy-3,4-dimethyl-6-benzyl- or -6-dimethylbenzyl-2-pyridone or 1-hydroxy-4-methyl-6-(β-phenylethyl)-2-pyridone.

The term "saturated" in this case designates those radicals which contain no aliphatic multiple bonds, i.e. no ethylenic or acetylenic bonds.

The abovementioned compounds of the formula I can be employed either in free form or as salts, use in free form is preferred.

If organic bases are used, poorly volatile bases are preferably employed, for example low molecular weight alkanolamines such as ethanolamine, diethanolamine, N-ethylethanolamine, N-methyldiethanolamine, triethanolamine, diethylaminoethanol, 2-amino-2-methyl-n-propanol, dimethylaminopropanol, 2-amino-2-methylpropanediol, triisopropanolamine. Further

poorly volatile bases which may be mentioned are, for example, ethylenediamine, hexamethylenediamine, morpholine, piperidine, piperazine, cyclohexylamine, tributylamine, dodecylamine, N,N-dimethyldodecylamine, stearylamine, oleylamine, benzylamine, dibenzylamine, N-ethylbenzylamine, dimethylstearylamine, N-methylmorpholine, N-methylpiperazine, 4-methylcyclohexylamine, N-hydroxyethylmorpholine. The salts of quaternary ammonium hydroxides such as trimethylbenzylammonium hydroxide, tetramethylammonium hydroxide or tetraethylammonium hydroxide can also be used, furthermore guanidine and its derivatives, in particular its alkylation products. However, it is also possible to employ as salt-forming agents, for example, low molecular weight alkylamines such as methylamine, ethylamine or triethylamine. Suitable salts for the compounds to be employed according to the invention are also those with inorganic cations, for example alkali metal salts, in particular sodium, potassium or ammonium salts, alkaline earth metal salts such as, in particular, the magnesium or calcium salts, as well as salts with bi- or tetravalent cations, for example the zinc, aluminum or zirconium salt.

The active compounds to be employed in the preparations of the compound of the formula I can be prepared, for example, according to processes given in US 2 540 218.

For the use according to the invention of the compounds mentioned, liquid to semisolid pharmaceutical preparations, in particular hair lotions, shampoos, liquid soaps, as well as cream, ointment and gel preparations, are suitable.

In this case, these are always preparations which, depending on their actual intended use, are applied to the skin and/or to the scalp for a shorter or longer time. Due to the addition of the compounds according to the invention, an effective treatment of the seborrheic dermatitis is brought about.

If the preparations according to the invention are present as shampoo, they can be in clear liquid or opaque liquid form, in cream form or even gelatinous. The surfactants on which these shampoos are based can be of

anionic, cationic, nonionic or amphoteric nature and can also be present as a combination of these substances.

Preferably, however, anionic surfactants are employed on their own or as a mixture with other anionic surfactants as base surfactants - if appropriate with addition of amphoteric surfactants as cosurfactant.

As the sole detergent substances, amphoteric surfactants are virtually insignificant, since their foaming behavior, thickenability and partly also skin and eye mucous membrane tolerability are only moderate. In combination with various anionic surfactants, however, precisely these properties are synergistically improved. This explains the relatively great importance of the amphoteric surfactants for the optimization of anionic shampoo bases.

Nonionic surfactants can also be employed as cosurfactants.

Examples of anionic detergent substances of this type which may be mentioned are: (C_{10}-C_{20})-alkyl- and -alkylenecarboxylates, alkyl ether carboxylates, fatty alcohol sulfates, fatty alcohol ether sulfates, alkylolamide sulfates and sulfonates, fatty acid alkylamide polyglycol ether sulfates, alkanesulfonates and hydroxyalkanesulfonates, olefinsulfonates, acyl esters of isothionates, α-sulfofatty acid esters, alkylbenzosulfonates, alkylphenol glycol ether sulfonates, sulfosuccinates, sulfosuccinic acid hemiesters and diesters, fatty alcohol ether phosphates, protein-fatty acid condensation products, alkylmonoglyceride sulfates and sulfonates, alkylglyceride ether sulfonates, fatty acid methyltaurides, fatty acid sarcosinates or sulforicinoleates. These compounds and their mixtures are used in the form of their water-soluble or water-dispersible salts, for example the sodium, potassium, magnesium, ammonium, mono-, di- and triethanolammonium as well as analogous alkylolammonium salts.

Examples of amphoteric surfactants which can be added to the shampoos are: N-((C_{12}-C_{18})-alkyl)-β-aminopropionates and N-((C_{12}-C_{18})-alkyl)-β-iminodipropionates as alkali metal and mono-, di- and trialkylolammonium salts; N-acylamidoalkyl-N,N-dimethylacetobetaine, preferably N-((C_8-C_{18})-acyl)amidopropyl-N,N-dimethylacetobetaine; (C_{12}-C_{18})-alkyldimethylsulfopropylbetaine; amphoteric surfactants based on imidazoline

(trade name: Miranol®, Steinapon®), preferably the sodium salt of 1-(β-carboxymethyloxyethyl)-1-(carboxymethyl)-2-laurylimidazolinium; amine oxides, e.g. (C_{12}-C_{18})-alkyldimethylamine oxide or fatty acid amidoalkyldimethylamine oxide.

Suitable nonionic surfactants which can be employed as detergent substances are, for example: fatty alcohol ethoxylates (alkyl polyethylene glycols); alkylphenol polyethylene glycols; alkylmercaptan polyethylene glycols; fatty amine ethoxylates (alkylamino polyethylene glycols); fatty acid ethoxylates (acyl polyethylene glycols), polypropylene glycol ethoxylates (Pluronic®); fatty acid alkylolamides (fatty acid amide polyethylene glycols); sucrose esters; alkyl polyglucosides; sorbitol esters and polyglycol ether.

Suitable cationic surfactants are, for example, quaternary ammonium salts such as di-((C_{10}-C_{24})-alkyl)dimethylammonium chloride or bromide, preferably di-((C_{12}-C_{18})-alkyl)dimethylammonium choride or bromide; (C_{10}-C_{24})-alkyldimethylethylammonium chloride or bromide; (C_{10}-C_{24})-alkyltrimethylammonium chloride or bromide, preferably cetyltrimethylammonium chloride or bromide and (C_{20}-C_{22})-alkyltrimethylammonium chloride or bromide; (C_{10}-C_{24})-alkyldimethylbenzylammonium chloride or bromide; preferably (C_{12}-C_{18})-alkyldimethylbenzylammonium chloride; N-((C_{10}-C_{18})-alkyl)pyridinium chloride or bromide, preferably N-((C_{12}-C_{16})-alkyl)pyridinium chloride or bromide; N-((C_{10}-C_{18})-alkyl)isoquinolinium chloride, bromide or monoalkylsulfate; N-((C_{12}-C_{18})-alkylolaminoformylmethyl)pyridinium chloride; N-((C_{12}-C_{18})-alkyl)-N-methylmorpholinium chloride, bromide or monoalkylsulfate, N-((C_{12}-C_{18})-alkyl)-N-ethylmorpholinium chloride, bromide or monoalkylsulfate; (C_{16}-C_{18})-alkylpentaoxethylammonium chloride; diisobutylphenoxyethoxyethyldimethylbenzylammonium chloride; salts of N,N-diethylaminoethylstearylamide and -oleylamide with hydrochloric acid, acetic acid, lactic acid, citric acid, phosphoric acid; N-acylamidoethyl-N,N-diethyl-N-methylammonium chloride, bromide or monoalkylsulfate and N-acylamidoethyl-N,N-diethyl-N-benzylammonium chloride, bromide or monoalkylsulfate, where acyl is preferably stearyl or oleyl.

The preparations according to the invention can additionally contain further additives, e.g. aromatic substances, colorants, opacifiers and pearl luster

agents, for example esters of fatty acids and polyols, magnesium and zinc salts of fatty acids, dispersions based on copolymers, thickeners such as sodium, potassium or ammonium chloride, sodium sulfate, fatty acid alkylolamides, cellulose derivatives of natural gums, collagen hydrolyzates, furthermore fats, oils, fatty alcohols, silicones, substances having a keratolytic and keratoplastic action, for example sulfur, salicylic acid or enzymes.

The shampoos are prepared in a manner known per se by mixing together of the individual components and a further processing - if necessary - suited to the particular type of preparation. Some of these various possible preparations are described by way of example in the working examples.

The preparations according to the invention can also be present in the form of aqueous and aqueous-alcoholic hair lotions, and also those in gel form and in aerosol form as spray or foam. Alcohols employed are preferably ethanol and isopropyl alcohol.

Further preparations which may be mentioned in which the 1-hydroxy-2-pyridones can be used according to the invention are, for example, cream and ointment preparations, products which are primarily used for the treatment of hairless head and body parts.

The preparation of all these preparations is also carried out - as already mentioned in the case of shampoo - in a manner known per se with addition of the active compound employed according to the invention. Of the abovementioned 1-hydroxy-2-pyridones, the preparations according to the invention can contain one compound or even several in combination.

The pH of the preparations is in the skin-physiological range of approximately pH 4.5 to 6.5. Whereas, when using the compounds in salt form, the adjustment of the pH range mentioned has to be carried out using organic acids, this measure is not necessary when using the free compounds.

In the preparations according to the invention, the active compounds is incorporated in amounts which are customarily between approximately 0.05 and approximately 10%. Within this range, the concentrations of the specific preparations depend on their intended use. Certain preparation

forms such as concentrates, which are to be diluted before use, can have considerably higher concentrations.

If they are preparations which remain on the skin and on the scalp, for example gel preparations, ointments, creams or hair lotions, lower concentrations will be employed, for example from about 0.05% to about 1%, preferably from 0.1 to 0.5%. In higher concentrations, they will expediently be used when they are preparations which, optionally after dilution, only act on the scalp for a short time, for example shampoos or liquid soaps. In these cases, for example, concentrations of approximately 0.2 to approximately 10%, preferably from approximately 0.5% to approximately 2%, can be expedient.

The following quantitative data relate to the weight, if not stated otherwise.

Example 1

A preparation according to the invention has the following composition:

Shampoo

(based on anionic detergent substances)

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone	1.00%
Sodium lauryl diglycol ether sulfate (27% strength solution)	40.00%
Disodium lauryl polyglycol ether sulfosuccinate (33% strength solution)	10.00%
Sodium chloride	2.50%
Water	46.50%

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Example 2

A preparation according to the invention has the following composition:

Shampoo

(based on anionic detergent substance with amphoteric surfactant as cosurfactant)

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone	1.00%
Sodium lauryl diglycol ether sulfate (27% strength solution)	36.00%
Cocamidopropylbetaine (30% strength solution)	6.00%
Sodium chloride	3.30%
Water	53.70%

Example 3

A preparation according to the invention has the following composition:

Shampoo

(based on anionic detergent substance with nonionic surfactant as cosurfactant)

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone	1.50%
Sodium lauryl diglycol ether sulfate (27% strength solution)	30.00%
Lauryl alcohol polyglucoside	8.00%
Sodium chloride	2.00%
Water	58.50%

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Example 4

A preparation according to the invention has the following composition:

Liquid soap

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone	1.00%
Sodium lauryl diglycol ether sulfate (27% strength solution)	35.00%
Cocamidopolyglycol ether sulfate magnesium salt (30% strength solution)	8.00%
Cocamidopropylbetaine (30% strength solution)	10.00%
Lauryl alcohol glycol ether	2.00%
Sodium chloride	2.00%
Water	42.00%

Example 5

A preparation according to the invention has the following composition:

Hair lotion

1-Hydroxy-4-methyl-6-[4-(4-chlorophenoxy)phenoxymethyl]-2(1H)pyridone	0.05%
2-Propanol	60.00%
Water	39.95%

Example 6

A preparation according to the invention has the following composition:

Gel preparation

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone	0.75%
2-Propanol	15.00%
2-Octyldodecanol	7.50%
Carbomer 4,000,000	0.50%
Polysorbate 60	1.50%
Sodium hydroxide	0.18%
Water	74.57%

Example 7

A preparation according to the invention has the following composition:

Cream preparation

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)-pyridone, aminoethanol salt 1:1	1.00%
2-Octyldodecanol	7.50%
Liquid paraffin	7.50%
Stearyl alcohol	7.50%
Cetyl alcohol	7.50%
Polysorbate 60	3.00%
Sorbitan monostearate	2.00%
Lactic acid, 90% strength	0.51%
Water	63.49%

Example 8

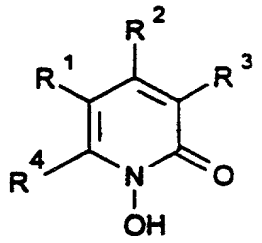
In a clinical study with a total of 180 patients, it was possible to show that the symptoms of seborrheic dermatitis of the scalp (severe scaling, inflammation, itching) can be effectively treated by a 1-2 × weekly treatment with a 1% strength ciclopirox shampoo preparation over a period of 4 weeks.

Example 9

In a clinical study, it was possible to successfully treat 180 patients with seborrheic dermatitis of the scalp, of the face and of the upper body by application of a 0.77% strength ciclopirox gel preparation over a period of 4 weeks.

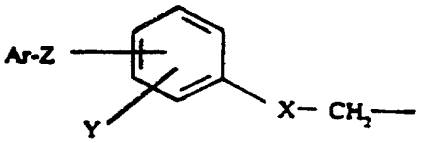
Patent claims:

1. The use of 1-hydroxy-2-pyridones of the formula I



(I)

in which R^1, R^2 and R^3, which are identical or different, are a hydrogen atom or alkyl having 1-4 carbon atoms, and
R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms or a radical of the formula II



(II),

where

X is S or O,

Y is a hydrogen atom or up to 2 halogen atoms such as chlorine and/or bromine,

Z is a single bond or the bivalent radicals O, S, $-CR^2-$ (R = H or (C_1-C_4)-alkyl) or other bivalent radicals having 2-10 carbon and, if appropriate, oxygen and/or sulfur atoms linked in the form of a chain, where - if the radicals contain 2 or more oxygen and/or sulfur atoms - the latter must be separated from one another by at least 2 carbon atoms and where 2 adjacent carbon atoms can also be linked to one another by a double bond and the free valences of the carbon atoms are saturated by H and/or (C_1-C_4)-alkyl groups,

Ar is an aromatic ring system having up to two rings which can be substituted by up to three radicals from the group consisting of fluorine, chlorine, bromine, methoxy, (C_1-C_4)-alkyl, trifluoromethyl and trifluoromethoxy, in free or in salt form,

for the production of a pharmaceutical for the treatment of seborrheic dermatitis.

2. The use as claimed in claim 1, wherein the compound of the formula I is employed in which Ar is a bicyclic system which is derived from biphenyl, diphenylalkane or diphenyl ether.

3. The use as claimed in claim 1 or 2, wherein the compound of the formula I contains a cyclohexyl radical in the position R^4.

4. The use as claimed in one or more of claims 1 to 3, wherein the compound of the formula I contains an octyl radical of the formula $-CH_2-CH(CH_3)-CH_2-C(CH_3)_3$ in the position R^4.

5. The use as claimed in claim 1, wherein 1-hydroxy-4-methyl-6-[4-(4-chlorophenoxy)phenoxymethyl]-2(1H)pyridone, 1-hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone or 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)pyridone is employed.

6. The use as claimed in one or more of claims 1 to 5, wherein the pharmaceutical is a hair lotion, shampoo or a cream, ointment or gel preparation.

7. The use as claimed in claim 6, wherein anionic, cationic, nonionic or amphoteric surfactants are employed on their own or as a mixture with other surfactants.

8. The use as claimed in claim 7, wherein the surfactant employed is at least one anionic surfactant on its own or as a mixture with other anionic surfactants and/or amphoteric surfactants.

9. The use as claimed in one or more of claims 1 to 8, wherein the pharmaceutical has a pH of 4.5 to 6.5.

10. A pharmaceutical preparation comprising a 1-hydroxy-2-pyridone of the formula I as claimed in claim 1 and at least one anionic, cationic, nonionic or amphoteric surfactant or a mixture of these surfactants.

11. A pharmaceutical preparation as claimed in claim 10, wherein the surfactant employed is at least one anionic surfactant on its own or as a mixture with other anionic surfactants and/or amphoteric surfactants.

12. A pharmaceutical preparation as claimed in claim 10 or 11, wherein the preparation has a pH of 4.5 to 6.5.

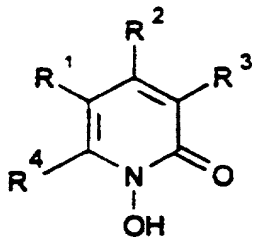
13. A pharmaceutical preparation as claimed in one or more of claims 10 to 12, wherein the 1-hydroxy-2-pyridone of the formula I is employed in a concentration of 0.2% to 10%, preferably of 0.5% to 2%.

COPY SENT TO PCT

Abstract

Use of 1-hydroxy-2-pyridones for the treatment of seborrheic dermatitis

Compounds of the formula I



(I)

are suitable for the production of pharmaceuticals for the treatment of seborrheic dermatitis.

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COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Use of 1-hydroxy-2-pyridones for the treatment of saborrheic dermatitis

the specification of which is attached hereto
/ was filed on September 16, 1997 as International Patent Application PCT/EP97/05070
I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

09/508,168 09 Feb 2000

Prior Foreign Application(s) for which Priority is Claimed:

Federal Republic of Germany, 19639818.5 of September 27, 1996

And I hereby appoint
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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